Treatment of Eczema Herpeticum
With Acyclovir

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- Eczema herpeticum is a serious herpes simplex virus infection that may have a fatal outcome. Effective antiviral therapy is therefore imperative. Acyclovir (9-[2-hydroxyethoxymethyl]-guanine) is a new antiviral agent with high potency and low toxic effect. We treated three cases of eczema herpeticum successfully with acyclovir.

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Eczema herpeticum, or Kaposi's varicelliform eruption due to herpesvirus hominis, is an uncommon disease usually found in individuals with atopic dermatitis. The disease is most frequently caused by a primary or recurrent infection with herpesvirus hominis type 1, but herpesvirus hominis type 2 may also be the responsible agent.

The severity of eczema herpeticum ranges from mild and transient to fatal. Some of the fatalities are due to viremia with the resultant infection of internal organs such as the lungs, brain, liver, gastrointestinal tract, and adrenal glands. The exact mortality of the disease is unknown, but with the advent of modern antimicrobial treatment, it has been well below 10% although secondary bacterial infection may still contribute to a fatal outcome. Attempts to treat eczema herpeticum with a variety of measures, especially antiviral agents, have been reported. The use of topical idoxuridine therapy, local applications of methylene blue in combination with light therapy, systemic cytarabine therapy, and vidarabine therapy have all been described.

In this article, we describe the use of acyclovir (9-[2-hydroxyethoxymethyl]-guanine), a new antiviral agent with low toxic effect, in the treatment of three patients with eczema herpeticum.

REPORT OF CASES

Case 1.—A 21-year-old man who had had atopic dermatitis since 2 years of age was hospitalized with acute dermatitis and illness. Four days before admission, nonitching vesicles had appeared on his cheeks. The following day, he had felt ill and had a temperature of 38.4 °C. Over the next few days, the vesicles appeared over his face, neck, shoulders, the upper part of the chest, and the upper arms. He had not been vaccinated recently against smallpox and had not been in contact with anyone who had recently received a smallpox vaccination. Neither the patient nor anyone in his family had a history of recurrent herpes simplex infection.

On admission, examination disclosed an ill young man with a temperature of 38.8 °C. His face, particularly around the eyes, and his neck, shoulders, the upper part of the chest, and the upper arms, were diffusely covered with round, approximately 3-mm vesiculopustular lesions, all in the same stage of development (Fig 1). He also had periorbital edema and blepharitis. Corneal sensitivity was normal bilaterally, and there were no signs of keratitis, as
Fig 1.—Appearance of patient 1 before treatment.

Fig 2.—Appearance of patient 1 nine days after initiation of acyclovir therapy.

judged by fluorescence testing. Enlarged submandibular lymph nodes were palpable. Typical eczematous patches of atopic dermatitis were present in the popliteal areas and over the ankles. The remainder of the physical findings were normal. Routine hematologic and serological studies gave normal results, except for a slight (subsequently transient) elevation of the transaminase values.

Bacteriologic cultures of material from the nose and skin lesions yielded Staphylococcus aureus and Streptococcus hemolyticus group B; both organisms were sensitive to erythromycin. A Tzanck smear of the contents of a vesicle showed multinucleated giant cells. A biopsy specimen from an active skin lesion showed a circumscribed area of epidermal cell degeneration with nuclear inclusion bodies, the formation of multinucleated giant cells, acantholysis, and necrosis with ulceration. These histological alterations were considered to be characteristic of a herpes simplex vesicle. Microscopic examination of the adjacent skin showed a mild chronic dermatitis compatible with the changes of chronic atopic dermatitis.

Because of a presumed bacterial component to the infection, the patient began treatment with erythromycin, 1 g/day orally, at the time of admission. Once the diagnosis of eczema herpeticum was confirmed by the findings on the Tzanck test and virological cultures, acyclovir was given intravenously (IV), starting on the third hospital day, in a dosage of 500 mg three times a day (20 mg/kg) for five days. Within 24 hours after initiation of treatment, the patient’s temperature became normal and he felt better. No new lesions appeared after this treatment was started. Local treatment consisted of 5% sulfur cream and wet gauze pads applied to his edematous eyelids four times a day. Nine days after institution of acyclovir therapy, all vesicles and crusts had healed (Fig 2).

The virological findings in this case are illustrated in Fig 3. Samples for virus isolation taken from the base of a lesion at the time of admission and on the fourth day of treatment were positive for herpesvirus in tissue culture. Culture of a specimen taken on the sixth hospital day showed no growth. Antibody titers, determined by the immune-adherence hemagglutination test to herpesvirus hominis type 1, rose from 64 on the first day to 512 after two weeks. IgM antibodies against herpes simplex virus were not detectable.

Case 2.—One week before admission, an 11-year-old girl, who had had atopic dermatitis and asthma since infancy, had played with a child with a herpes infection on her lips. Two days later, a vesicle developed on the patient’s lower lip. Three days thereafter, multiple vesicles appeared over her body and her temperature rose to 40 °C. On admission to the hospital, examination disclosed that the entire skin surface was covered with vesiculopapular lesions that contained a clear fluid; all were in the same stage of development. The popliteal areas, ankles, wrists, and elbows showed typical lesions of atopic dermatitis. The physical findings were otherwise normal. A Tzanck smear of a vesicle showed multinucleated giant cells. Bacteriologic culture of material from the skin lesions yielded S
Antibodies to Herpesvirus in Serum

Virus Isolation + + -

Temperature, °C
39 38 37 36

Days
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16

Vesicles Crusts Healing

Acyclovir, 500 mg Three Times a Day

Erythromycin, 250 mg Four Times a Day

Fig 3.—Clinical course and virological findings in patient 1.

Case 3.—A 10-year-old boy, known to suffer from atopic dermatitis, was admitted to the hospital acutely ill, with a vesicular rash on his face and a temperature of 40.1 °C. Three days before admission, he had had a temperature of 39.0 °C; a rash had appeared on the same day. On examination, his face was covered with clear vesicles, all in the same stage of development. There was severe periorbital edema. The other physical findings were normal. He was treated with acyclovir, 250 mg IV three times a day (20 mg/kg) for five days. No antibiotic therapy was given. The temperature dropped to normal within 24 hours; after six days, all of the skin lesions had healed. On the second day of treatment, he had a transient hallucinatory state; no neurological abnormalities were found. A spinal tap was done. The CSF demonstrated no abnormalities, and immunofluorescence of the CSF showed no evidence of CNS herpes infection. Skin samples for virus isolation, taken on the first and third days of treatment, were positive for herpesvirus, but thereafter were negative. Antibody titers to herpesvirus hominis type 1 rose from 0 to 32 after two weeks. IgM antibodies against herpes simplex virus showed a titer of 62.

COMMENT

Because of a certain, albeit low, mortality, eczema herpeticum may be a serious disease. Effective treatment of the patient is directed toward the prevention of viremia and involvement of internal organs, and the control of secondary bacterial infection. At present, there are four antiviral agents to be considered for use in patients with serious herpesvirus infections: idoxuridine, vidarabine, interferon, and acyclovir. The experience with new drugs, such as bromovinyl deoxyuridine and phosphonoformic acid (foscarnet sodium is the international proprietary name for the trisodium salt), is still too limited to consider them for clinical use. Systemic idoxuridine toxic effect permits only topical applications of the drug, and it seems doubtful that a local agent could prevent viremia as effectively as one given systemically.

Systemic cytarabine has been claimed to be effective in the treatment of eczema herpeticum, but it can no longer be recommended for antiviral treatment because it has proved to be more toxic than vidarabine. Even so, vidarabine has a number of serious side effects, including nausea, vomiting, diarrhea, tremors, thrombocytopenia, and leukocytopenia; neurological abnormalities have also been observed. Recently, the treatment of eczema herpeticum with vidarabine has been reported. Unfortunately, both patients died of bacterial septicemia.

Interferon given in high doses might have beneficial effects in the treatment of eczema herpeticum, but we found no reports of its successful use for this infection. Interferons are difficult to obtain and expensive. The selection of an appropriate interferon and its effective dosage pose difficult problems.

Acyclovir (9-[2-hydroxyethoxymethyl]-guanine) is a new antiviral agent with low toxicity for normal cells and greater inhibitory activity against herpesvirus hominis than any compound previously studied. In vitro, acyclovir is converted to a monophosphate by a virus-specific thymidine kinase; subsequently, it is converted into diphosphate and...
triphasic form, acyclovir acts by inhibiting viral DNA polymerase 30 times more strongly than it inhibits normal cellular DNA polymerase. The inhibition of viral DNA polymerase selectively stops replication of the infecting herpesvirus. In studies done in mice, rabbits, and guinea pigs, acyclovir has been shown to be effective in the treatment of encephalitis, keratitis, and skin lesions caused by a herpesvirus.\textsuperscript{13-15} In man, the treatment results in viral pneumonia, mucocutaneous herpes simplex infection, and herpes zoster infection with acyclovir have been reported.\textsuperscript{16-18} The first and impressive results of controlled trials of the drug in herpes simplex and herpes zoster infections have recently been published.\textsuperscript{19-22} These well-controlled clinical trials demonstrated strong antiviral effects of acyclovir, in contrast to the largely anecdotal efficacy of the aforementioned antiviral drugs claimed for the treatment of eczema herpeticum.

For the three patients described in this article, the institution of acyclovir therapy had a dramatic effect on body temperature and the cutaneous lesions. In each case, the rapid cessation in the spread of the eruption and the overall clinical improvement in the patient's condition during the first days of treatment were impressive. As the secondary bacterial infection played a minor role in cases 2 and 3, no antibiotics were given. Nevertheless, the body temperature and skin condition improved very rapidly during the treatment course with acyclovir in both of these patients. In cases 2 and 3, IgM antibodies against herpes simplex virus were detectable, indicating a primary infection with the herpes simplex virus.

Compared with other antiviral drugs, acyclovir seems to be remarkably free of side effects to date. Transient impairment of renal function, transient rises in transaminase levels, and delirium have been reported.\textsuperscript{19,21,22} In our patients, the slight elevation of transaminase values in patient 1 and the hallucinatory state in patient 3 should probably be ascribed to acyclovir, although the possibility that these effects were produced by the virus itself cannot be completely ruled out. Nonetheless, the potential toxic effect of the drug cannot be fully evaluated as yet because of its still limited use.

Acyclovir seems to be an effective antiviral agent that deserves a place in the treatment of serious herpesvirus infections.

Erik Scheffer, MD, interpreted the histological findings. Werner A. Herrmann, MD, treated patient 3.

References